## REMARKS

Claims 23, 25-31 and 33-70 are pending in this application. Claims 23, 41 and 49 have been amended to remove "or animal" in the claims which were not deleted in the previously filed amendment. Claims 25, 31, 35, 40, 43, 48, 52, and 57 have been amended to separate administrations recited therein. The recitations deleted from the claims have been added to new claims 59-66, respectively. Claims 34 and 42 have been amended to separate tumors recited therein. The recitations deleted from the claims have been added to new claims 67-70, respectively. No new matter has been added.

The claims encompass methods for inhibiting tumor formation in humans, methods for inhibiting metastasis of tumors in humans, and methods for reducing the recurrence of tumors in humans, using an effective amount of thalidomide.

### Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn

Remaining rejections in this case relate to allegations, on the part of the Examiner, that the method claims are unpatentable under 35 U.S.C. § 103(a) over Sugiura, *et al.* ("Sugiura"), United States Patent No. 5,399,363 to Liversidge *et al.* ("Liversidge"), Mückter, or Grabstald *et al.* ("Grabstald"). Applicant respectfully traverses. In particular, Applicant respectfully asserts that the Examiner is improperly considering only selected teachings in the art, improperly dismissing art that teaches away (*e.g.*, Grabstald) as opinion, and erroneously interpreting Liversidge as teaching that thalidomide is an anticancer agent. Each is addressed in detail below.

When the art is considered as a whole as dictated by the Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), the Examiner's rejection must be withdrawn. The overwhelming majority of the art teaches away from the use of thalidomide as an anticancer agent. As the Examiner is well aware, after the tragedies that occurred with thalidomide in the late 1950's, the mechanism of action of thalidomide was extensively investigated including possibility that its mechanism of action will yield a cytotoxic agent that is useful for treatment of cancer. As the Examiner is also aware, the investigations notwithstanding, thalidomide was never developed as an anticancer agent. Indeed, even the Sloan-Kettering Institute for Cancer Research (*See*, articles authored by doctors of Sloan-Kettering Institute, *e.g.*, Sugiura *et al.* and Grabstald *et al.*) did not further pursue, much less develop, thalidomide as an anticancer agent (despite the Examiner's interpretation of their work as positive). Significantly, Applicant has cited published studies contradicting the very

work relied upon by the Examiner to sustain her rejection. Applicant offers additional publications not already of record that teach away from the invention and submits Supplemental Information Disclosure Statement together with List of References Cited.[1]

In sum, the art relied upon by the Examiner shows that animal models failed to provide any promise for thalidomide as an anticancer agent. *In re Fine,* 837 F.2d 1071, 1075. And, the papers reporting on human experience with thalidomide concluded that it was ineffective in treating cancer. As a result, the Examiner's rejection cannot be sustained.

Applicant will now address each reference cited in the Office Action specifically and point out the Examiner's errors of fact and law.

**Sugiura Fails to Render the Claims Obvious**

In an attempt to rebut Sugiura's clear teaching that thalidomide is an **in**effective anticancer agent based upon animal data, the Examiner states that "no one compound is effective against all cancers" and "a compound can be operative against one or more kinds of cancer while being inoperative against others" (page 2 of the Office Action). Applicant does not disagree. However, Sugiura does not teach or suggest what cancers, if any, thalidomide might be used for. Instead, it teaches those which thalidomide is not useful for. At most, Sugiura is a 1964 invitation to experiment with thalidomide in certain unknown cancer cases. This is not the proper legal standard for a finding of obviousness. *In re O'Farrel,* 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

Furthermore, the Examiner's reasoning demonstrates that one of ordinary skill in the art would not have been provided with a reasonable expectation of success based upon Sugiura. For this reason alone the rejection must be withdrawn. *In re Fine,* 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Applicant respectfully submits (a) that the Examiner has cited nothing in the prior art that suggests modifying the teachings of Sugiura to obtain the claimed methods and (b) that the prior art does not provide one of ordinary skill in the art with a reasonable expectation of success. Thus, Applicant respectfully requests that the rejection over Sugiura be withdrawn.

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[1] Applicant notes that some of references cited in IDS are not discussed herein. Applicant requests that all the references be made of record in the file history of the application and that the Examiner execute the 1441 Form enclosed.

**The Art as a Whole Prior to this Invention Contradicts Any Alleged Teaching in Sugiura that Thalidomide is Effective Against Some Cancers**

The Examiner must consider the state of the art as a whole prior to the earliest effective filing date of the case at hand (March 1, 1993). *In re Dow Chemical Co.*, 5 U.S.P.Q.2d at 1531 (Fed. Cir. 1988). Thus, it is improper to view the disclosure of a single prior art reference separately from the teachings of others in the relevant art. The Examiner must consider Grabstald and other art at the time as a whole. Indeed, as the pending claims require the treatment of human cancers, Grabstald, which relates to investigations involving human cancer patients, is arguably more relevant than the animal data in Sugiura.

The Examiner contends that the teaching away of Grabstald, "in the absence of more definite evidence of pharmacologic or anticancer effects in man, we conclude that further random trials of this drug against cancer in man are not indicated," is not persuasive, on the ground that it is an opinion (page 3, first paragraph of the Office Action). It is improper for the Examiner to disregard the relevant published literature as mere "opinion." *In re Zurko,* 258 F.3d at 1385, 59 U.S.P.Q.2d at 1697. First, if the Examiner wishes to do so, she must put it in an Examiner's declaration or affidavit in accordance with MPEP 2144.03. C. *See*, 37 C.F.R. §1.104(d)(2); *Cf. In re Sang-Su Lee* 277 F.3d 1338, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002). Second, what the Examiner refers to as mere "opinion" is a peer relevant article by medical doctors at Sloan-Kettering Institute based upon experience with human cancer patients. The Supreme Court mandates consideration of this teaching in an obviousness context. *Graham v. John Deere,* 383 U.S. 1,148 U.S.P.O. 459 (1966). The Examiner cannot simply disregard it as "opinion."[2]

Grabstald allegedly discloses three independent clinical studies using thalidomide in 71 patients with certain types of cancers. In detail, Grabstald purportedly makes disclosures, on left column of page 301, as follows:

> "***Therapeutic activity on cancer***. *No definite clinical responses* were observed in the patients treated in Series B. One patient with endometrial carcinoma did not show any apparent progression of the disease for several months during the treatment. There was, however, no decrease in the size of abdominal masses, and after several months the growth of the cancer became apparent and the patient died one year after the onset of therapy. This course

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[2] The very essence of scientific research is "opinion." The Examiner cannot simply refuse to consider research conclusion that she may not agree with.

is not incompatible with the natural evolution of untreated disease. One case of endometrial carcinoma in each of the other two series showed no effect.

In Series C *no objective improvement* was observed in any of the 28 patients.

In Series A *only 1 of 30 patients* demonstrated objective benefit conceivably related to the administration of thalidomide."

Grabstald contradicts any allegation that thalidomide is an effective anticancer agent. Grabstald teaches away from the claimed invention of inhibiting tumor formation or metastasis in humans. Significantly, one of ordinary skill in the art would not have taken any expectation of successfully practicing the claimed invention from the reference. *In re Fine,* 837 F.2d 1071, 1075.

The Examiner further alleges that the data in Grabstald show that thalidomide is effective against certain cancers, which would lead one of ordinary skill in the art to conclude that it can be used to treat them. (page 3, first paragraph of the Office Action). This statement, which is made without factual support,[3] is contrary to the plain disclosure of Grabstald, as the reference allegedly concludes that "no significant degree of antineoplastic activity was demonstrated." (Grabstald, last paragraph of right column, page 301). The Examiner has cited no portion of Grabstald showing that thalidomide is effective against any particular cancer in man. Aside from this contradiction, it is well established that an examiner's unsupported and conclusory statements cannot support a rejection under § 103. *In re Sang-Su Lee*, 277 F.3d at 1343-4 (a *prima facie* case of obviousness "must be satisfied with factual and objective evidence found in the prior art"). For these reasons, the rejection of obviousness over Sugiura, particularly in view of the teaching away of Grabstald, should be withdrawn.

**Grabstald Fails to Suggest the Claimed Invention**
**and does Not Provide a Reasonable Expectation of Success**

Further, all of the pending claims are rejected as allegedly unpatentable under 35 U.S.C. § 103(a) over Grabstald on the ground that it allegedly discloses (page 301) the

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[3] To the extent these assertions are based on the Examiner's personal knowledge, Applicants respectfully request that such knowledge be supported by an affidavit. 37 C.F.R. § 1.104(d)(2).

disappearance of pulmonary metastases in a patient using thalidomide (page 3, third and fourth paragraphs of the Office Action). Applicant respectfully traverses this rejection.

Contrary to the Examiner's contention, Grabstald allegedly discloses that only one patient with renal cell carcinoma showed regressions of pulmonary metastases after nephrectomy[4] and that six patients with renal cell carcinoma treated with thalidomide showed no evidence of benefit. (Grabstald, page 301, right column, second paragraph). Grabstald concluded that "no evidence of objective regressions was obtained, with exception of one patient with renal cell cancer whose pulmonary metastases disappeared transiently after treatment. Since this patient also had a nephrectomy preceding the regression, the response may be attributed to this operation." (Grabstald, last paragraph, page 302). Therefore, Grabstald provides no evidence that thalidomide's use resulted in disappearance of any metastasis. In fact, Grabstald teaches away from Applicant's invention by demonstrating that many patients did not respond.

In other words, the Examiner has not shown that Grabstald would have provided those skilled in the art with any suggestion of the claimed invention, motivation to modify or combine the cited references, much less with the legally required reasonable expectation of success. Thus, Applicant respectfully requests that the rejection over Grabstald be withdrawn.

**The Animal Studies of Mückter Alone Neither Suggest the Invention nor Provide A Reasonable Expectation of Success**

Next, all of the pending claims are rejected as allegedly unpatentable under 35 U.S.C. § 103(a) over Mückter on the ground that "Mückter discloses (page 533, both columns) that the latent period of manifestation of tumors increased with thalidomide and that thalidomide retarded in a most impressive fashion the manifestation and growth of tumors induced in rats by the carcinogen DMBA." (Page 3 of the Office Action). Applicant respectfully traverses this rejection.

Applicant respectfully submits that, similar to Sugiura, Mückter investigated thalidomide in animals such as rats and mice, but not in human cancer patients. Significantly, the prior art arguably more relevant to the pending claims relates to human studies, *e.g.*, Grabstald that taught away from Applicant's invention, as discussed above.

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[4] The term "nephrectomy" means excision of a kidney, according to Dorland's Medical Dictionary, 23rd Ed., page 460.

Even if Mückter is considered as a relevant reference, it is clear that the animal studies reported therein do not suggest the claimed use of thalidomide in humans.

First, Mückter discloses that, "in contradiction to rat experiments, mice affected with mammary carcinoma died relatively quickly from the carcinoma. Figures 11 and 12 show that thalidomide did not influence in a lasting way either number or the growth of tumors in the mice." (Pages 537-8 of Mückter). In other words, the mice study in Mückter failed to suggest any utility of thalidomide in humans.

Mückter further describes that no effects of thalidomide on transplanted tumors were observed in nearly all of the experiments performed prior to the filing of the invention. (Page 531 of Mückter). It is also noted in Mückter that Sugiura showed no effect on twenty-four tumors of mouse, rat and hamster, and merely a weak effect for Lewis Bladder-carcinoma. Table 1, page 531 of Mückter. It is well settled that a prior art reference must be considered in its entirety when relied upon by a rejection under 35 U.S.C. § 103. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.* 277 U.S.P.Q. 657 (Fed. Cir. 1985). Therefore, those skilled in the art would not recognize from Mückter that thalidomide would be effective in inhibiting tumor formation or growth in humans. One skilled in the art would not have been motivated to use thalidomide in the claimed methods. Further, one of ordinary skill in the art reading Mückter would not have taken any expectation of successfully practicing the claimed invention. Thus, Mückter cannot support the Examiner's obviousness rejection in view of all the relevant literature.

**Liversidge's Misleading Statement does not Render the Claimed Invention Obvious**

Finally, the Examiner contends that the Applicant's arguments, that at the time of Liversidge, thalidomide was not considered useful for the treatment of cancer, are not persuasive, on the ground that it allegedly discloses that thalidomide is an anticancer agent (page 3, second paragraph of the Office Action). Applicant respectfully traverses this rejection.

At the time of Liversidge, thalidomide was not known to be an anticancer agent, as is clear from the teachings of Grabstald and other studies discussed above. Liversidge's misleading statement does not change that fact. The portion in Liversidge relied upon states "the anticancer agent can be an immunosuppresive drug, such as, for example, cyclosporine, azathioprine, sulfasalazine, methoxsalen, and thalidomide." (Column 3, lines 46-49.) First, this statement does not teach or suggest that thalidomide is an anticancer agent.

It allegedly states merely that an "anticancer" agent[5] may be an immunosuppressive drug and that thalidomide is an immunosuppressive drug. At best, Liversidge suggests that immunosuppressive drugs can be tried in Liversidge's delivery method. Further, the terms of anticancer agent and immunosuppressive drugs used in Liversidge are only his own lexicography, and are not supported by any sound scientific evidence. For example, according to The Merck Index, at the time and after Liversidge's disclosure, thalidomide was therapeutically classified only as an immunomodulatory compound and a sedative. (The Merck Index, 12th ed., Whitehouse Station: Merck , 1996). Neither of these therapeutic uses teach or would suggest that thalidomide would have been useful in the claimed method. Nowhere in Liversidge are the immunosuppressive drugs specifically shown to be effective in treating or preventing cancers. Without such teachings or suggestions of anticancer activity of thalidomide, one skilled in the art would not have been motivated to use thalidomide in the claimed methods. The Examiner's unsupported allegation fails to provide the requisite legal suggestion, and is premised on unsound basis. The examiner's statement is nothing but conclusory opinion and it cannot form a basis for obviousness rejection. *In re Sang-Su Lee*, 277 F.3d 1338, 1343-4 (Fed. Cir. 2002).

Further, the Examiner has not established that the prior art provided one of ordinary skill in the art with a reasonable expectation of success. *See In re Fine,* 837 F.2d at 1075. At most, Liversidge suggests that immunosuppressive agents can be incorporated into the delivery method of nanoparticles that Liversidge discloses. The statement provides, at most, a mere invitation to experiment. As the Examiner is aware, an allegation that something may have been "obvious to try" cannot form an adequate basis for a rejection under § 103. *In re O'Farrel,* 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

The Examiner is reminded that Liversidge must be read in the context of what was known by those of ordinary skill in the art prior to the invention. It must be read in conjunction with other references such as Sugiura, Grabstald, Mückter and other art available at that time. *See, In re Ochiai*, 71 F.3d 1565, 1569, 37 USPQ2d 1127, 1131 (Fed. Cir. 1995). As discussed above, Sugiura, Grabstald and Mückter as well as other references teach away from the claimed invention. Liversidge does not provide any evidence to the contrary. Thus, Liversidge, alone or in combination with other references, does not render the claimed

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[5] Applicants may be their own lexicographers and define "black" as "white." However, this does not make black in fact white.

invention obvious. Applicant respectfully submits that the rejection over Liversidge be withdrawn.

In sum, all the references cited by the Examiner, alone or in combination with others, do not render the claimed invention obvious. Applicant respectfully submits that the rejections under 35 U.S.C. § 103(a) be withdrawn.

**The Examiner Here Improperly Failed to Consider**
**Arts That Teaches Away From the Claimed Invention**

Several published articles disclosing that thalidomide would not be or was not useful for a treatment of cancer have not been considered by the Examiner. Such articles are discussed herein and are provided in a Supplemental Information Disclosure Statement.[6]

Applicant directs the Examiner's attention to DiPaolo, *Cancer Chemotherapy Reports*, No. 29, p. 99-102, 1963, "Effect of Thalidomide on a Variety of Transplantable Tumors." DiPaolo tested thalidomide in standard transplantable rodent tumors, and several tumor systems of mesenchymal, trophoblastic and embryonic origin (p. 99). The results, according to DiPaolo, indicate that thalidomide is **in**effective against transplantable cancers in animal studies and that thalidomide **never** produced complete inhibition or regression of the established hetero-transplants. (Tables 1 and 2, from p. 99, right column, the 2nd last paragraph to p. 102).

DiPaolo also reported that thalidomide was **in**effective against Ehrlich Ascites tumor in different *in vitro* tests and *in vivo* tests. *See*, Table II and page 387, left column, first paragraph, DiPaolo, *Proceedings of the Society for Experimental Biology & Medicine*, 1963, v114, pg. 384-387, "*In vitro* Test Systems for Cancer Chemotherapy, II. Correlation of *in vitro* Inhibition of Dehydrogenase and Growth with *in vivo* Inhibition of Ehrlich Ascites Tumor." *See also*, DiPaolo, June 26, 1964, "Thalidomide: Effects on Ehrlich Ascites Tumor Cells *in vitro*." Given the overall teaching away of DiPaolo, it contradicts the Examiner's contention and it does not provide one of ordinary skill in the art with a reasonable expectation of success in achieving the claimed intention. *In re Fine,* 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

Further, Applicant directs the Examiner's attention to Bach. Bach carried out experiments on anti-carcinogenic effects of thalidomide on a carcinoma and a leukemia in

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[6] Although prior art of human studies is more relevant to the claimed invention, because the Examiner relies on animal studies in the office action, Applicant also cites and discusses references on animal studies.

mice. Daily treatment with thalidomide did **not** show any inhibitory effect on the tumor growth in all of the experiments, even with very large doses in some cases. A. Bach, *The Lancet*, No. 1271, pg. 71, June 8, 1963, "Thalidomide in Cancer Chemotherapy." *See also*, A. Bach, *Acta Pathologica Et Microbiologica Scandinavica*, 1963 (59), pg. 491-499, "Studies on the Possible Anti-Neoplastic Effect of Thalidomide" (p. 495 and 498). Clearly, Bach demonstrated that thalidomide was **not** active against cancer and teaches away from the claimed invention.

Roe *et al.* discusses biological activity such as carcinogenicity of thalidomide. It lists a variety of studies which obtained negative results of tumor-inhibition by thalidomide. F. J. C. Roe and B. C. V. Mitchley, *Nature*, Volume 200, pg. 1016-17, December 7, 1963, "Thalidomide and Neoplasia." It describes that the authors observed **no** inhibition of growth of the transplantable Walker rat carcinosarcoma 256 with repeated large doses of thalidomide; that Roath *et al.* observed an inhibition of some aspects of cellular activity in leucocyte cultures exposed to thalidomide, but the significance of their findings has been disputed; and that Lüers found **no** evidence that thalidomide causes mutations in *Drosophila* (p. 1017, left column, first paragraph). The prior art as a whole suggests that thalidomide is not effective against cancer.

In addition, Chaundhry reported that thalidomide failed to show any influence on induced tumors when given to hamsters using three dosage levels, a single 5 or 10 mg dose, and a 5mg initial injection plus 5mg/week. *See*, Chaundhry, *Cancer Research*, 1966, 26 part 1, 1884-86, "Effect of Prednisolone and Thalidomide on Induced Submandibular Gland Tumors in Hamster." Further, Gershbein demonstrated that thalidomide had **no** effect in the total number of colon adenocarcinomas and their occurrence in the proximal and distal portions of male rats fed a basal diet supplemented with 0.10% each of thalidomide. *See*, Gershbein, *Cancer Letters*, 1991, 60: 129-133, "The thalidomide analog, EM 12, Enhances 1,2-Dimethylhydrazine-Induction of Rat Colon Adenocarcinomas." The overall teaching of the animal studies discussed above provides additional evidence of non-obviousness of the claimed invention.

In light of the disclosures of all the relevant literature, one of skill in the art would not find the cited references to provide any suggestion of the claimed invention, motivation to modify or combine the references, much less with the legally required reasonable expectation of success. Therefore, the claimed invention is not obvious in view of the art as a whole.

## The Rejection Under Obviousness-Type Double Patenting Should Be Withdrawn

On pages 3-4 of the Office Action, the pending claims are rejected under the judicially created obviousness-type double patenting over claim 1 of U.S. Patent No. 5,629,327 ("the '327 patent"). Applicant respectfully traverses this rejection.

The Examiner alleges that the conflicting claims are not patentably distinct from each other, because the '327 patent discloses a method of using thalidomide to treat undesired angiogenesis and thalidomide inhibits cancer by preventing said undesired angiogenesis. Claim 1 of the '327 patent is directed to a method of treating undesired angiogenesis in a human or animal comprising administering to the human or animal with the undesired angiogenesis a composition comprising an angiogenesis-inhibiting amount of thalidomide. The Examiner has not demonstrated that claim 1 of the '327 patent teaches or suggests the methods of inhibiting tumor formation and tumor metastasis in humans using thalidomide as recited by the pending claims. Applicant asserts that the pending claims of the invention are different and patentably distinct from claim 1 of the '327 patent. No *prima facie* case of obviousness has been established by claim 1 of the '327 patent. Applicant respectfully requests that the rejection of the pending claims under judicially created obviousness-type double patenting be withdrawn. Applicant further submits that no terminal disclaimer over the cited patent is necessary.

## Conclusion

Applicant respectfully requests that the above amendment and remarks be entered in the file of this application. Should the Examiner not agree that all claims are allowable, then a further personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application. No fee is believed due. However, please charge any required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date January 27, 2005

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